Remarks

Reconsideration of this application, as amended, is respectfully requested. Claims 1-4, 6-12, and 14-18 are now pending. New independent claim 18 has been added; claim 13 was previously withdrawn from consideration.

Independent claims 1, 6 and 14 are currently amended to recite that all or part of a non-adhesive surface of a support having electrostatic properties is directly covered with at least one biologically active substance or allergen in the absence of added gel, where the biologically active substance or allergen is in the form of individualized or agglomerated particles that are kept in contact with the non-adhesive surface of the support by electrostatic forces of attraction between the particles and the support.

The current amendment of claims 1, 6 and 14 is fully supported by the instant specification at page 7, line 37, to page 8, line 5. Support for new claim 18 may be found throughout the entire specification, including, for example, page 2, lines 22 and 26, as well as in present claim 6.

Claims 1-4, 6, 8, 10-12 and 14-17 have been rejected under 35 USC §103(a) as being unpatentable over Fischer, U.S. Patent No. 4,836,217 ("Fisher"), in view of Antelman, WO/2001/049302 ("Antelman") and Peck, U.S. Patent No. 4,821,733 ("Peck")

Also, claims 7 and 9 have been rejected under 35 USC §103(a) as being unpatentable over Fischer, Antelman and Peck as applied to claims 1-4, 6, 8, 10-12 and 14-17 above, and further in view of Lipper et al. WO 02/076379 ("Lipper").

We respectfully request reconsideration of the present application, based on the foregoing amendment of the claims and the remarks that follow. In particular, we submit the patch as presently claimed is not obvious over the prior art, which fails to suggest the use of electrostatic forces to maintain an active substance in the form of particles on the surface of a skin patch. As will be discussed below, no prior art references disclosed or suggested a skin patch to directly deliver a substance in its reactogenic state, nor how such a skin patch could be made.

Fischer relates to a patch comprising an active substance mixed with a polymer having film-forming properties, this polymer allowing the homogeneous distribution of the substance on

the patch. Thus, as in the FINN-CHAMBERS patch, the active substance in Fischer has to be dissolved or dispersed in a gel prior to be spread out on the carrier of the patch, where it is maintained through adhesive properties of the gel.

By contrast, the present invention provides for the active substance in the form of individualized or agglomerated dry particles, to be directly maintained on the support by electrostatic forces of attraction between these particles and the support, i.e., without any addition of gel. Skin patches containing an active substance in its reactogenic state of origin (e.g., with no added gel) had never been disclosed or suggested in the art prior to the present invention. Furthermore, it was not known in the art how to make such skin patches, and the ability to use electrostatic forces according to the present invention was totally unexpected.

The Examiner has acknowledged in the Office Action that "*the reference to electrostatic properties and forces are not taught expressly by Fischer*" (see top of page 6 of the OA). Applicants agree with this assertion and further point out that Fischer is totally silent about the use of electrostatic forces to maintain a substance on the surface of a patch. Furthermore, Fischer fails to suggest the use of an active substance in the form of particles (i.e., devoid of gel). It is thus submitted that Fischer, either alone or in combination with any other references of record, fails to teach the invention as defined in the claims.

Fischer fails to teach the use of an active substance in the form of particles that are attached directly on the surface of the support of the patch. In Fischer, the substance is always dispersed in a film (see e.g., column 3, line 63, "*The vehicle will be selected from among substances having film-forming properties*", column 4, lines 58-60, "*it has been found essential to choose a film-forming polymer capable of...*", column 5 lines 58-60, "*the test substance is added to a film forming polymer*" ; claim 1 "*said film containing as the film-forming substance a film-forming polymer*", etc.) Accordingly, (i) the substance is not in direct contact with the support, (ii) the substance is not in the form of free particles, but embedded in a solid film .

In the Office Action, the Examiner called attention to the fact that the abstract of Fischer describes the test substance as being incorporated in a dry film. Even if dry, the film maintains the substance in a non natural conformation. In addition, the substance is not in direct contact with the support but is embedded in a film which can alter its state. Furthermore, as disclosed at

column 3, lines 62-68, the film-forming polymeric vehicle is used "together with a volatile liquid such as e.g. water will give a gel or coalescable emulsion in which the substance can be distributed homogeneously in a dissolved, crystallized, micronized, emulsified or dispersed state..." (emphasis added). Accordingly, during manufacturing, the substance is dissolved prior to any deposition and Fischer does not disclose or suggest a patch covered with a substance in the form of particles, nor the advantage of using such a patch, nor how this can be accomplished.

Fischer is totally silent about the use of electrostatic forces to maintain a substance on the surface of a patch. In fact, Fischer never refers to electrostatic forces. As mentioned above, this was acknowledged by the Examiner : "*the reference to electrostatic properties and forces are not taught expressly by Fischer*" (see top of page 6 of the OA). Furthermore, Fischer clearly indicates that the nature of the support of the patch is not important (see column 5, lines 33-34: "*the choice of film carrier material is not in any way critical to the invention*"). Such a statement by Fischer clearly emphasizes the fact that the nature of the interaction between the film and the support cannot be electrostatic.

In the Office Action, the Examiner quoted column 5, lines 43-56, of Fischer. In this section, Fischer provides that a polyester film may be treated for a short period of time in an "electric field (e.g., corona discharge treatment)". According to the Examiner, "the above explanation would be recognized by the skilled artisan as an example of electrostatic support according to the definition disclosed in the instant specification." The applicants respectfully disagree. The techniques of corona discharge treatment or introduction of polar structures into a film have nothing whatsoever to do with the electrostatic properties of a support; they are in fact methods for improving the wettability of a polymeric support by liquids. This is further discussed in the attached Declaration by Dr. Bertrand Dupont, an inventor in this application. As indicated by Dr. Dupont, in section A of the Declaration, the treatment in a Corona discharge chamber does not create electrostatic forces in the support, but increases hydrophilicity of the support. Thus, it is simply incorrect to argue that Fischer teaches the use of electrostatic forces. In Fischer, the substance is embedded in a gel, and the gel is maintained by adhesive properties of the gel on the surface of the support. While the support may be treated in a Corona discharge chamber, this simply increases hydrophilicity but in no way creates electrostatic forces. Fischer

fails to teach how to obtain a patch with an active substance in a dry and native form and as individualized or agglomerated particles.

From the foregoing, it is clear that Fischer fails to teach or suggest a patch as presently claimed, in which the active substance is in the form of particles (i.e., devoid of any gel). Fischer fails to suggest the use of the substance in such state, and fails to teach how such a substance can be maintained on the surface of the support.

The deficiencies in Fischer cannot be cured by any other references of record. Indeed, none of these references disclose the use of a substance in dry form, nor the use of electrostatic forces as a means to maintain such a substance on a support.

Antelman relates to a pharmaceutical composition used to enhance skin growth, in particular, for the treatment of burns or skin grafts. The disclosed composition comprises at least one electron active compound, preferably Ag4O4, and at least two polyvalent cations. The electron active compound is believed to operate against pathogens "by transferring electrons between their lower-valent ions and their higher-valent ions in the crystal, thereby contributing to the death of pathogens by traversing their cell membrane surface. It would seem that this, in effect, 'electrocutes' the pathogens" (page 14, last paragraph). Accordingly, in Antelman, the reference to electrostatic forces only designates the mode of action of the drug. It has nothing to do with a method of coating a patch support.

It was acknowledged in the Office Action that Antelman does not teach an atopy (sensitization) patch. In further contrast to the teaching of Antelman, the invention proposes to use electrostatic forces to maintain an active substance on a patch support. Contrary to the assertion in the office action, Antelman does not "adequately describe the nature of electrostatic forces and properties of bioactive particles in regard to dermal patches which are facilitated by the patch design." The combination of Antelman and Fischer would not teach the present invention, but would lead, at best, to a patch in which a drug of Antelman is embedded in a gel and immobilized on a support through covalent linkage.

Peck relates to a transdermal detection system comprising a compound that is able to react with the targeted substance that migrates to the surface of the skin, thereby producing a detectable signal such as coloration or pH variation. However Peck contains no disclosure about

electrostatic forces or other means for maintaining an active substance in the form of individualized or agglomerated dry particles on a patch support.

Lipper discloses a transdermal system for the delivery of drugs in the form of a printed temporary tattoo, wherein a dye can be used as an indicator of the drug absorption. As with Peck, however, there is no teaching in Lipper regarding electrostatic forces or other means for maintaining an active substance in the form of individualized or agglomerated dry particles on a patch support.

Accordingly, the disclosures of Antelman, Peck and Lipper, considered alone or in combination, fail to remedy the severe deficiencies of Fischer with respect to the skin patch of the present invention. Indeed, none of the cited references teaches or suggests the use of electrostatic properties of a support to obtain a skin patch wherein an active substance in the form of individualized or agglomerated particles is maintained in contact with the support by electrostatic forces of attraction between these particles and the support without any addition of gel.

The use of the active substance in the form of particles (i.e., without any addition of gel) according to the present invention is particularly advantageous to prevent any alteration of the native state or properties of this active substance. This is particularly important when the active substance is an allergen. In this case, even a minor modification in the structure of the allergen can be detrimental for the immunogenicity of this molecule, and thus for the efficiency of the desensitization method using the patch. In the Office Action, the Examiner asserted that the claimed invention is a mere variation of the Finn Chambers patch that, absent unexpected results, would be obvious over Fischer. Applicants strongly disagree. The claimed device is not a mere variation of the Finn Chambers. It is a completely novel approach for making patches. The use of an active substance in the form of particles had never been proposed before and represents a very substantial improvement over all prior patch technologies, which used either liquid substances or gels. The use of the substance in form of a powder increases the stability, avoids denaturation, and allows better dosing. The use of a powder is also much more convenient from an industrial prospective. The ability to use the substance in the form of particles, directly coated and maintained on a support, is in itself unexpected. No one had ever attempted such approach in the art and it could not be expected that the substance could be maintained under suitable conditions

on the surface of a support to form a patch. The invention is not a mere variation; it is a technological breakthrough.

In this regard, it should be noted that a patch according to the claims is presently on the market under commercial name diallerterst®. This is illustrated in the attached brochure "diallerterst® food tolerance test: a DBV technologies product.", which emphasizes the efficacy and innovative concept of the claimed skin patch.

The attached scientific publication by Kalach et al. (**JACI** 116 (2005) pp1321-1326), further emphasizes the advantages of the electrostatic patch of the present invention over the Finn Chambers patch. In this article, a pilot study of the usefulness and efficacy of the electrostatic patch of the present invention (designated ready-to-use APT) versus the Finn Chambers was conducted in 49 children. As concluded by the authors, "*the ready-to-use APT exhibited versus the comparator a significantly higher sensitivity (76% vs 44%) and test accuracy (82.9% vs 63.4%)*" (see page 1325, right column, last paragraph, emphasis added). This is also stated e.g., page 1323, right column last paragraph). These results are unexpected.

Also, the attached Declaration by Bertrand Dupont further illustrates the benefits provided by the skin patch of the present invention over the prior art. As described in section B, ¶11, of the Declaration, a first patch covered with powdered milk containing beta-lactoglobulin, a milk protein, was maintained for 3 months at 25°C and 60% relative humidity under non-airtight conditions, after which the beta-lactoglobulin remaining, as measured by radial immunodiffusion, amounted to less than 0.5% of the total protein content. As further described in section B, ¶12, a second patch covered with powdered milk containing beta-lactoglobulin was maintained for 2 months at 40°C under dry conditions, after which the quantity of beta-lactoglobulin remaining, as measured by radial immunodiffusion, amounted to about 3.5% of the total protein content. A comparison of the test results described in ¶11 and ¶12 provides a clear demonstration of the deleterious effect of adding a liquid or a gel on the stability of an active substance, in particular, a protein.

A patch as described in Fischer or the FINN-CHAMBERS patch thus has a substantially shorter period of effectiveness than the patch of the invention. Moreover, for most proteins, the absence of gel is essential to preserve the native state of the active substance and thus provides a

patch having a period of efficiency compatible with the commercialization of a ready-to-use form. As disclosed above, when tested on 49 human subjects, a patch as presently claimed exhibited versus the FINN CHAMBERS a significantly higher sensitivity (76% vs 44%) and test accuracy (82.9% vs 63.4%).

For all of the aforementioned reasons, independent claims 1, 6, 14 and 18 are believed to be allowable over the applied prior art. Dependent claims 2-3, 7-12 and 15-17, all of which ultimately depend from one of the independent claims, are also allowable for the same reasons. Applicants further request that withdrawn claim 13, which is dependent upon independent claim 6 and therefore inherently allowable with claim 6, be reinstated and likewise allowed.

This application is believed to be in condition for allowance, and prompt action to this effect is respectfully requested. If, after consideration of this response, the Examiner has any remaining questions about the allowability of this application, he is requested to call Applicants' representative at the telephone number shown below.

The Commissioner is authorized to charge U.S. Deposit Account No. 08-1935 in the amount of $245.00 for the two-month extension and $110.00 for extra independent claim. If any additional fees are due, or an overpayment has been made, please charge, or credit, our deposit account number 08-1935.

Respectfully submitted,

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